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⑬ Applicant: OTSUKA PHARMACEUTICAL  
FACTORY, INC.  
115, Aza Kuguvara  
Tateiwa  
Muya-cho  
Naruto-shi  
Tokushima 772 (JP)  
Applicant: OTSUKA PHARMACEUTICAL CO.,  
LTD.  
9, Kandatsukasa-cho 2-chome  
Chiyoda-ku  
Tokyo 101 (JP)

⑭ Inventor: IGUCHI, Seiichiro  
87-5, Aza-Hamabatanishi,  
Saida,  
Muya-cho,  
Naruto-shi,  
Tokushima 772 (JP)  
Inventor: HIGASHINO, Rika  
1-3, Aza-2-bu,  
Shinkiral,  
Kitajima-cho  
Itano-gun,  
Tokushima 771-02 (JP)

⑮ Representative: Hansen, Bernd, Dr.  
Dipl.-Chem. et al  
Hoffmann, Eitlie & Partner,  
Patentanwälte,  
Arabellastrasse 4  
D-81925 München (DE)

⑯ MEDICAL MATERIAL AND PROCESS FOR PRODUCING THE SAME.

⑰ A medical material comprising a polymer or copolymer of a polar vinyl derivative and containing an antithrombocytic agent. Since it can release the antithrombocytic agent in an effective concentration for long, it has a high anticoagulant effect and the effect of preventing platelet loss by activating the same.

**EP 0 665 023 A1**

## TECHNICAL FIELD

The present invention relates to a medical material such as a medical device which directly contacts with blood, and a process for producing the same. More particularly, it relates to a medical material which causes no blood coagulation (thrombogenesis) or platelet loss due to activation of platelet even if the material directly contacts with blood, and a process for producing the same.

## BACKGROUND ART

In the medical field, thrombogenesis on the surface of polymer materials used for an artificial heart, artificial lung, vascular prosthesis, catheter, etc., which directly contact with blood is a serious problem. Therefore, medical materials having excellent anticoagulant or anti-thrombogenic activity have been required.

As a method for imparting the anti-thrombogenic activity to medical materials, for example, there have hitherto been known a method(1) of forming a composite of heparin and a polymer material, or a method(2) of immobilizing fibrinolytic enzyme to the surface of a polymer material [for example, see Japanese Laid-Open Patent Publication No. 54-68097 (Japanese Patent Publication No. 60-40861), Japanese Laid-Open Patent Publication No. 56-136564 (Japanese Patent Publication No. 59-51304), Japanese Laid-Open Patent Publication No. 57-75655 (Japanese Patent Publication No. 61-6662) and Japanese Laid-Open Patent Publication No. 57-14358 (Japanese Patent Publication No. 63-43107)].

However, the above method (1) has a problem that, there are large restrictions on processing and manufacturing because heparin is thermally unstable, and that sustained release for a long period of time can not be expected because the retention amount of heparin in the material is small.

Further, the above method (2) has a problem that, there are extremely large restrictions on manufacturing because the processing is conducted by surface coating and the treatment is complicated and, further, fibrinolysis activity is liable to be deteriorated by heat, and that sustained effect can not be expected because the absolute amount of a fibrinolytic enzyme in the material is small.

Further, safety of a chemical structure, which is used for a ligand or spacer in case of formation of composite or immobilization, to the human body has not been worked out completely, at present.

On the other hand, materials superior in blood compatibility have also been developed so as not to cause thrombogenesis.

For example, in the field of vascular prosthesis, a vascular prosthesis comprising an expanded

poly(tetrafluoroethylene) manufactured by Gore Co., U.S.A. is known. However, in these materials, it is indispensable to produce a porous structure by expanding in order to develop the anti-thrombogenic activity, which results in large restrictions on use application and production process.

Further, a medical material of the polyurethane or polyurethane urea having a microdomain structure, however, the material has a problem that the production process is complicated because of its hard thermal molding, which results in large restrictions on manufacturing, and that constant anti-thrombogenic activity can not be easily obtained because the microdomain structure varies largely depending upon the processing method.

Furthermore, a medical material wherein an antiplatelet agent is blended in a polyurethane or polyurethane urea is proposed, however, the material has a problem that the production process is complicated because of its difficult thermal molding, which results in large restrictions on manufacturing.

On the other hand, it is known that a HEMA (2-hydroxyethyl methacrylate)-styrene copolymer having a microdomain structure has anti-thrombogenic activity. However, it is limited to the coating material because of its small mechanical strength and the field of application is limited to a specific one.

It is a main object of the present invention is to provide a medical material which solves the above technical problems and can be easily produced, and which can uniformly contain an antiplatelet agent and enables continuous release of the antiplatelet agent, and a process for producing the same.

## DISCLOSURE OF THE INVENTION

In order to solve the above problems, the present inventors have intensively studied about formation of composites of various drugs and polymer materials. As a result, it has been found that it is possible to formulate an antiplatelet agent, particularly cilostazol, dipyridamole or aspirin in a polymer or copolymer of a vinyl derivative having a polar group, and that a release rate of the antiplatelet agent can be optionally controlled depending upon a kind of the above polymer or copolymer, amount or blending method of the antiplatelet agent, blending of at least one of additive to the polymer or copolymer and the like. Thus, the present invention has been accomplished.

That is, the present invention provides a medical material comprising a polymer or copolymer of a vinyl derivative having a polar group, said polymer or copolymer containing an antiplatelet agent.

### BRIEF EXPLANATION OF DRAWINGS

Fig. 1 is a graph illustrating a variation with time in dissolution concentration of drug obtained by using the respective films produced in Examples 1, 2 and 3.

Fig. 2 is a graph illustrating a variation with time in dissolution concentration of drug obtained by using the respective films produced in Examples 4 and 5.

Fig. 3 is a schematic diagram illustrating the equipment used in Example 7.

Fig. 4 is a graph illustrating a variation with time in dissolution concentration of drug obtained by using the respective films produced in Examples 12 and 13.

Fig. 5 is a graph illustrating a variation with time in dissolution concentration of drug obtained by using the film produced in Example 18.

Figs. 6 (a), (b) and (c) are respectively sectional, side and elevational views illustrating the blood circuit connector for pump-oxygenator produced in Example 22.

### DETAILED EXPLANATION OF THE INVENTION

Examples of the polar group include hydroxyl group, chlorine atom, cyano group, alkoxy carbonyl group and the like.

Examples of the polymer or copolymer of the vinyl derivative having the polar group include polyvinyl chloride, polyvinyl alcohol, polyacrylonitrile, polymethacrylate, polyacrylate, vinyl chloride-vinylidene chloride copolymer, ethylene-vinyl alcohol copolymer and the like. In the present invention, it is particularly preferred to use polyvinyl chloride, ethylene-vinyl alcohol copolymer, polymethacrylate, polyacrylate or polyacrylonitrile, more preferably polyvinyl chloride, ethylene-vinyl alcohol copolymer or polymethacrylate. These polymers or copolymers may be used as they are as a main constituent material of the medical material, or they may be used by applying (coating) on or impregnating into the other material. Further, these polymers or copolymers may be used alone, or two or more sorts of them can be combined by mixing or laminating.

The polymer or copolymer used in the present invention has hitherto been used as the material which directly contacts with blood, and it is proved that the polymer or copolymer has extremely high stability and safety. Besides, the polymer or copolymer is stably supplied and is inexpensive.

The polymer or copolymer of the vinyl derivative can be anyone which is suitable as the medical material, and those having various physical properties can be employed. For example, in case of polyvinyl chloride, those having an average degree

of polymerization of 800 to 8000, preferably 800 to 4500 are suitable. If necessary, there can be blended plasticizers such as di-2-ethylhexyl phthalate, di-n-decyl phthalate, tri-2-ethylhexyl trimellitate, etc., various stabilizers, secondary plasticizers, lubricants and the like.

On the other hand, in case of the ethylene-vinyl alcohol copolymer, the composition ratio of ethylene to the total amount of the medical material can be appropriately varied according to the usage of the medical material and processing method. Normally, it is preferred that the ethylene content is 10 to 80 molar %. When the ethylene content exceeds 80 molar %, blood compatibility and dispersibility of the antiplatelet agent becomes inferior. On the other hand, when the amount is smaller than 10 molar %, mechanical strength, water resistance and processing characteristics in a melting method described hereinafter are deteriorated. On the other hand, in case of polymethacrylate, polymethyl methacrylate) can be suitably used, and those having a low melting temperature are particularly preferred because processing due to the melting method can be easily conducted.

Examples of the antiplatelet agent include cilostazol, dipyridamole, aspirin, ticlopidine, beprasten, indomethacin, sulfapyrazone, satigrel, dindobufen, dazoxiben, furegrelate, ozagrel, pirmagrel, dazmegrel, midazogrel, daltroban, sulotroban, vapirost, clopidogrel, prostaglandin E<sub>1</sub>, iloprost, limaprost and the like. In addition to the above, there are 2-[4,5-bis(4-methoxyphenyl)thiazol-2-yl]pyrrole-1-acetic acid ethyl ester, 2-methyl-3-(1,4,5,6-tetrahydronicotinoyl)pyrazolo[1,5-a]pyridine, 1-(cyclohexylmethyl)-4-[4-(2,3-dihydro-2-oxo-1H-imidazo[4,5-b]quinoline-7-yl)-1-oxobutyl]piperazine, 3-methyl-2-(3-pyridinyl)-1H-indol-ocanoic acid, (E)-7-phenyl-7-(3-pyridyl)-6-heptenoic acid, (±)-6-(1-imidazolylmethyl)-5,6,7,8-tetrahydronaphthalene-2-carboxylic acid, 4-[α-hydroxy-5-(1-imidazolyl)-2-methylbenzyl]-3,5-dimethylbenzoic acid, 1-(2-carboxyethyl)-2-methyl-3-(1H-imidazol-1-ylmethyl)indole, (E)-1-[3-(phenylmethoxy)-1-octenyl]-1H-imidazole, 7-[2α,4α-(dimethylmethano)-6β-(2-cyclopentyl-2β-hydroxyacetamido)-1α-cyclohexyl]-5(Z)-heptanoic acid, (E)-11-[2-(5,6-dimethyl-1-benzimidazolyl)-ethylidene]-6,11-dihydrobenz[b,e]oxepin-2-carboxylic acid, 5-[(1R,6S,7S,8R)-8-hydroxy-7-(3S)-3-hydroxy-4,4-dimethyl-1,6-noradiynyl]-cis-bicyclo[4,3,0]non-2-ene-3-yl]-3-oxapentanoic acid, methyl 5-[(1S,5S,6R,7R)-7-hydroxy-6-[(E)-(S)-3-hydroxy-1-octenyl]bicyclo[3,3,0]oct-2-en-3-yl]-pentanoate, [1α,2α(Z),3β,4α]-(+)-7-(3-[(phenylsulfonyl)amino]-bicyclo[2,2,1]hept-2-yl)-5-heptenoic acid, (-)-cis-3-acetoxy-5-[2-(dimethylamino)ethyl]-2,3-dihydro-8-methyl-2-(4-methylphenyl)-1,5-dibenzothiazepine-4-(5H)-one

and the like. They can be used alone or in combination thereof. Among them, cilostazol, dipyridamole, beraprost, sastigrel and aspirin can be suitably used. Particularly, cilostazol is preferred.

The amount of the antiplatelet agent is 0.01 to 60 parts by weight, preferably 0.1 to 50 parts by weight, more preferably 1 to 44.4 parts by weight, particularly 4.8 to 33.3 parts by weight, based on 100 parts by weight of the medical material comprising the polymer or copolymer of the vinyl derivative, which contains the antiplatelet agent. When the amount of the antiplatelet agent exceeds the above range, molding properties are inferior. If molding could be conducted, physical properties are deteriorated and, therefore, it is not suitable for practical use. On the other hand, when the amount of the antiplatelet agent is smaller than the above range, it becomes difficult to control release of the antiplatelet agent and anticoagulant effect is deteriorated, which results in no addition effect. Further, as described hereinafter, the release amount of the antiplatelet agent can be controlled by varying the amount of the antiplatelet agent within the above range. In general, there is an upper limit to the dispersion amount of the antiplatelet agent dispersed uniformly into the polymer or copolymer of the vinyl derivative. Within the range including the upper limit, the larger the amount, the greater the release rate of the antiplatelet agent. On the other hand, when the antiplatelet agent is contained in the large amount exceeding the above upper limit, the release rate is decreased after all. However, a duration time thereof is expected to be prolonged. Accordingly, it is desirable to select a suitable amount of the antiplatelet agent according to a kind, object or application use of the medical material to be produced.

The medical material of the present invention can be suitably used to, for example, a material for medical device. As an example of the medical device which can be produced by the material of the present invention, there are blood vessel catheter, cannula, monitoring tube, artificial kidney, pump-oxygenator, blood circuit for extracorporeal circulation, A-V shunt for artificial kidney, vascular prosthesis, artificial heart, artificial cardiac valve, temporary bypass tube of blood, blood line for hemodialysis, stent, blood bag, disposable circuit of blood cell separator, film or hollow fiber dialysis membrane and the like.

Hereinafter, the material of the present invention and a process for producing a device using the material of the present invention will be explained. Typical production process includes a solution method and a melting method. In the solution method, the polymer or copolymer of the vinyl derivative having the polar group and the antiplatelet agent are uniformly dissolved in a solvent

and then the solvent is removed to give a medical material of the present invention. Examples of the solvent include dimethylformamide, dimethylacetamide, dimethyl sulfoxide, cyclohexanone, tetrahydrofuran, chloroform, dichloromethane, acetone and 1,1,1,3,3-hexafluoro-2-propanol, and a mixed solvent of two or more sorts of them. Among them, tetrahydrofuran is preferable to polyvinyl chloride, 1,1,1,3,3-hexafluoro-2-propanol or dimethyl sulfoxide is preferable to ethylene-vinyl alcohol copolymer, and methylene chloride or chloroform is preferable to poly(methyl methacrylate), because the solvent can be easily distilled off and has high solubility.

It is preferred that the polymer or copolymer of the vinyl derivative to be used is sufficiently washed by a method such as Soxhlet extraction in advance to remove impurities in the polymer or copolymer. Further, it is preferred that it is sufficiently dried to remove water in the polymer or copolymer.

The molding can be conducted by casting a solution wherein the above respective components are dissolved in a solvent on a glass plate, extruding into a tubular extrudate or applying on the other structure, followed by removing the solvent. Thereby, the polymer or copolymer of the vinyl derivative can be made into a film-like or tubular form, or coated. The solvent can be removed by air-drying, drying with heating under reduced pressure, phase transition due to a solidifying solution and the like. Examples of the coagulating solution include poor solvents of the polymer or copolymer, e.g. water, alcohols such as methanol, ethanol, propanol, butanol, etc., ketones such as acetone, etc. In this case, it is necessary to prevent the antiplatelet agent from dissolving in the coagulating solution during coagulation of the polymer material in every way. Accordingly, when solvency of the antiplatelet agent to the poor solvent of the polymer material is large, it is preferred to use a coagulating solution wherein a solvent for reducing the solvency of the antiplatelet agent is mixed with the poor solvent of the polymer material to solidify the polymer material and the antiplatelet agent contained therein, simultaneously.

A manner of molding a tubular device by the solution method will be explained in detail hereinafter. Firstly, a solution wherein the above respective components are dissolved in a solvent is applied on the surface of a suitable stem and then dried to form a tube, which is stripped from the stem. Otherwise, the above solution is applied on the surface of the stem, which is dipped in a coagulation solution to coagulate the polymer on the surface of the stem to give a tube and, thereafter, the resulting tube is stripped from the stem and is dried. The tubular device can also be pro-

duced by drying after the solution was extruded into a hollow form in the solidifying solution. Furthermore, the tubular device can also be produced by coating on a ready-made device such as vascular prosthesis, blood circuit, blood line for hemodialysis, etc. according to a dipping method, vacuum method, gas compression transmission method, rotary drum method and the like.

When molding a film-like material by the solution method, for example, there can be used a method of molding into a film such as a method comprising casting a solution on a glass plate and then drying to remove the solvent, a method comprising coating a solution directly on a woven fabric, knitted web, non-woven fabric, etc., or impregnating the solution into a woven fabric, knitted web, non-woven fabric, etc., and then drying to remove the solvent and the like. Further, the film-like material can also be produced by provided with a coating to produce a ready-made film according to a dipping method, spraying method and the like. The film thus obtained can be further coated to produce a multi-layer film.

In the solution method, the rate of the antiplatelet agent released from a molded article can be controlled by varying the amount of the antiplatelet agent contained in the polymer or copolymer, kind of the polymer or copolymer or method of removing the solvent (e.g. a method of drying under normal or reduced pressure, or a method of coagulating using a coagulation solution) and the like. Particularly, when using soft polyvinyl chloride as polyvinyl chloride, the release rate can also be controlled by the blending of plasticizers, stabilizers, secondary plasticizers, lubricants and the like. In case of coating, the release amount can be controlled more precisely by repeating coating plural times and varying conditions such as amount described above. Particularly, in case of coating on the ready-made device, it is preferred that, regarding a device staying in a living body for a long period of time, multi-layer coating is conducted to make the amount of the platelet agent of the inner layer large and to make that of the outer layer small. This enables sustained release of drug for a long period of time while maintaining physical properties of the material.

The solution methods described above are particularly effective when using the drug which is thermally unstable as the antiplatelet agent.

On the other hand, in case of the melting method, the polymer or copolymer of the vinyl derivative having the polar group is mixed with the antiplatelet agent in a molten state to obtain a medical material of the present invention. The melting must be conducted so that the antiplatelet agent is uniformly dispersed in the polymer or copolymer without causing decomposition of the

antiplatelet agent. Therefore, a suitable antiplatelet agent and polymer or copolymer may be selected so that the polymer or copolymer is molten at a temperature lower than a decomposition temperature of the antiplatelet agent. Further, if necessary, oxidation of the antiplatelet agent or resin can be prevented if melting and molding operations are conducted in a non-oxygen atmosphere. It is preferred to remove water in the polymer or copolymer to be used as much as possible in view of stability of the drug and resin and accuracy of the molded article.

Various molding methods can be employed for the melting method, for example, a tubular or sheet-like molded article can be molded by an extrusion molding, and a molded article of a complicated structure can be molded by an injection molding. It is also possible to coat on a metal wire by using a crosshead.

The amount of the antiplatelet agent released from the molded article can also be controlled in melting molding by varying the amount of the antiplatelet agent in the polymer or copolymer, kind of the polymer or copolymer and the like. Particularly, when using polyvinyl chloride, it is possible to control release of the antiplatelet agent by the blending of additives such as plasticizers, stabilizers, secondary plasticizers, lubricants and the like, similar to the solution method. By conducting multi-layer (multi-color) molding and varying the amount or kind of the antiplatelet agent in the respective layers (parts), physical properties required for the medical material can be obtained and, at the same time, anticoagulant activity can be developed only at the desired part and the release amount can be controlled more precisely.

In the present invention, a particularly preferred combination is that of cilostazol as the antiplatelet agent and an ethylene-vinyl alcohol copolymer. Since cilostazol is superior in compatibility with the ethylene-vinyl alcohol copolymer, cilostazol can be uniformly dispersed. Also, cilostazol can be uniformly dispersed in soft polyvinyl chloride by adjusting the blending of additives.

The material molded into a tubular form of the present invention, particularly that in which the ethylene-vinyl alcohol copolymer is used can be suitably used as a blood circuit for extracorporeal circulation, catheter, bypass tube and the like. Examples thereof include a tube having a three-layer structure wherein an ethylene- $\alpha$ -olefin copolymer elastomer layer, a maleic acid-modified polyethylene layer and a cilostazol-containing ethylene-vinyl alcohol copolymer layer are laminated in order from the outer layer. On the other hand, those which are molded into a tubular form using soft polyvinyl chloride can be used as a blood circuit for extracorporeal circulation, or blood line for

hemodialysis, in addition to a catheter or a bypass tube. Further, a multi-layer tube of which layers have different compositions can be easily produced by molding using a multi-layer die.

When the material molded into a tubular form of the present invention is used for a peripheral circulation circuit during cardiopulmonary bypass, not only anticoagulant action but angiectatic action is developed by using cilostazol or dipyridamole as the antiplatelet agent to be blended. Therefore, circulatory failure of distal tissue caused by controlled shock can be improved, and it is more advantageous.

The material molded into a film-like form of the present invention can be used as a material for a blood bag, etc. Among them, a multi-layer film wherein a material having large gas permeability such as ethylene-vinyl acetate copolymer or ethylene- $\alpha$ -olefin copolymer is used is particularly preferable as a platelet storage bag.

The material molded into a filament by an extrusion molding or molded into a coil-like or zig-zag form by an injection molding of the present invention can be suitably used as it is or after knitting, as a vascular stent. In this case, when cilostazol is used as the antiplatelet agent, not only thrombogenesis at the surface of the stent but endothelial proliferation of blood vessel is inhibited, therefore it is particularly preferred to prevent reclosure of blood vessel. Further, it is possible to produce a vascular stent from a stainless steel or tantalum wire of which surface is coated with the material of the present invention, using a cross-head, thereby, those having the same effect as that described above can be obtained.

As described above, examples wherein the material of the present invention is used for the medical device itself were explained. As other examples, it is also possible to dispose the material of the present invention molded into any form in the medical device, as a member for developing antiplatelet action. For example, there can be used a method of encapsulating film-like or particulate small fragments of the material of the present invention in a ready-made platelet storage bag, a method of fixing small fragments of the material of the present invention at the upstream in an extracorporeal circulation circuit and the like.

As described above, regarding the material of the present invention, it is possible to control the release rate of the antiplatelet agent by varying the kind, amount or blending method of the antiplatelet agent, kind of polymer or copolymer, blending of the additive and the like. The release rate can also be controlled by varying the shape to be molded, particularly surface area.

## FIELD OF THE INDUSTRIAL APPLICABILITY

As described above, the medical material of the present invention has such an effect that it has high anticoagulate activity and inhibition action of platelet loss due to activation of platelet because the antiplatelet agent can be continuously dissolved in the effective concentration. Further, the process for producing the medical material of the present invention has such an effect that said material can be easily produced.

## EXAMPLES

The following Examples further illustrate the present invention in detail but are not to be construed to limit the scope thereof.

### Example 1

190 mg of soft polyvinyl chloride [comprising 100 parts by weight of polyvinyl chloride having an average degree of polymerization of 1300, 50 parts by weight of di-2-ethylhexyl phthalate (hereinafter referred to as "DOP"), 5 parts by weight of epoxidized soybean oil, 2.2 parts by weight of a stabilizer (mixture of calcium stearate and zinc stearate) and 0.1 parts by weight of a lubricant] and 10 mg of cilostazol were dissolved in 5 ml of tetrahydrofuran and the resulting solution was casted on a glass plate, which was allowed to stand at 40 °C for 5 hours under reduced pressure (-760 mmHg) to distill off tetrahydrofuran to give a transparent film. The amount of cilostazol for the resulting film was 5 % by weight.

### Example 2

According to the same manner as that described in Example 1 except that the glass plate on which the solution was casted was dipped in water at room temperature to cause coagulation and, after washing with water repeatedly, it was dried at 50 °C for 10 hours under reduced pressure (-760 mmHg), instead of distilling off tetrahydrofuran, a white film was obtained. The amount of cilostazol for the resulting film was 5 % by weight.

### Example 3

According to the same manner as that described in Example 1 except for using polyvinyl chloride containing 10 parts by weight of DOP, a transparent film was obtained.

100 Mg of the respective film obtained in Examples 1, 2 and 3 was collected, respectively, and charged in 10 ml of a normal saline (pH 7.4) heated to 37 °C in advance, and then shaken by a

thermostatic shaker at 37 °C. After shaking for one hour, a sample was taken out and charged in 10 ml of the other normal saline (pH 7.4) heated to 37 °C, and then shaken by a shaking apparatus at 37 °C for one hour. Thereafter, this operation was repeated for 8 hours to determine a variation with time in cilostazol concentration in a dissolution solution. The results are shown in Fig. 1.

As is apparent from Fig. 1, continuous dissolution of cilostazol in the concentration exceeding the effective concentration (1.1 µg/ml) is observed in all of films of Examples 1, 2 and 3 from the beginning of dissolution to 8 hours after that. Accordingly, it is found that the respective films of Example 1, 2 and 3 have high anticoagulant activity.

Further, there is a difference in removing method of solvent between Examples 1 and 2. Therefore, it is found that a difference in dissolution concentration of cilostazol observed is caused by the above difference, which results in difference in release properties.

Further, there is a difference in amount of plasticizer between Examples 1 and 3. Therefore, it is found that a difference in release properties is also caused by the above difference.

In case of soft polyvinyl chloride, it is anxious about dissolution of the plasticizer, however, no dissolution of the plasticizer was observed in all Examples. As a result, it was confirmed that selective dissolution (release) of cilostazol can be conducted.

A film was produced according to the same manner as that described in Example 1 except for changing the amount of cilostazol for the film of polyvinyl chloride to 10 % by weight. As a result, the resulting film was cloudy. It is considered that this is because cilostazol is contained in the amount exceeding the amount which causes a saturated state. Regarding the resulting film, the dissolution amount of cilostazol was examined according to the same manner as that described above. As a result, dissolution in the concentration exceeding the effective concentration was observed from the beginning of dissolution to 8 hours after that, however, the dissolution concentration was low in comparison with that of Example 1 (5 % by weight).

Further, when the amount of the plasticizer was increased, the resulting film became cloudy in the lower amount of cilostazol. In addition, when the resulting film is transparent and the amount of cilostazol is the same, the larger the amount of the plasticizer, the higher the dissolution concentration. Even if the polymerization degree of polyvinyl chloride to be used is varied, the amount of cilostazol which causes formation of the cloudy film is scarcely influenced.

#### Example 4

After 450 mg of an ethylene-vinyl alcohol copolymer (manufactured by the Nippon Synthetic Chemical Industry Co., Ltd.), ethylene content: 32 molar %) was molten with heating on a hot plate at 180 °C, cilostazol was added thereto. Immediately after that, the melt was kneaded with stirring and the resulting mixture was pressed by a pressing machine to give a film having a thickness of about 100 µm. The amount of cilostazol for the resulting film was 10 % by weight.

#### Example 5

According to the same manner as that described in Example 4 except for using 475 mg of an ethylene-vinyl alcohol copolymer and 25 mg of cilostazol, a film was obtained.

100 Mg of the respective film obtained in Examples 4 and 5 was collected, respectively, and then tested according to the same manner as that described in Examples 1, 2 and 3 to determine a variation with time in cilostazol concentration in a dissolution solution. The results are shown in Fig. 2.

As is apparent from Fig. 2, gentle decrease of the dissolution amount is observed, however, sustained release of cilostazol in the concentration exceeding the effective concentration (1.1 µg/ml) until 8 hours after the beginning of dissolution is observed. Accordingly, it is found that the films of Examples 4 and 5 have high anticoagulant activity. Further, it is found that, the larger the amount of cilostazol (Example 4), the higher the dissolution concentration.

In Example 4, a transparent film could be obtained even if the amount of cilostazol was increased, until the amount reaches 20 % by weight. However, when the amount exceeds 30 % by weight, a cloudy film was obtained. Further, the dissolution amount of cilostazol was determined according to the same manner as that described above. As a result, dissolution of cilostazol in the amount exceeding the effective concentration was observed from the beginning to 8 hours after that in all films. However, regarding the cloudy film, the dissolution concentration exceeding that of the transparent film containing 20 % by weight of cilostazol is not observed. Even if a kind of the ethylene-vinyl alcohol copolymer (e.g. ethylene content, molecular weight, saponification degree, etc.) was varied, the amount of cilostazol which causes formation of the cloudy film was scarcely influenced.

Example 6 (Production of blood bag)

To a film having a thickness of 250  $\mu\text{m}$ , which is composed of soft polyvinyl chloride [comprising 100 parts by weight of polyvinyl chloride having an average degree of polymerization of 1100, 50 parts by weight of DOP, 5 parts by weight of epoxidized soybean oil, 0.3 parts by weight of a stabilizer (mixture of calcium stearate and zinc stearate) and 0.1 parts by weight of a lubricant], a solution of polyvinyl chloride (comprising 100 parts by weight of polyvinyl chloride having an average degree of polymerization of 1100 and 40 parts by weight of DOP) and cilostazol (contained in an amount of 5 % by weight to a total solid content) in tetrahydrofuran (total concentration: 4 % by weight) was continuously sprayed and dried to provide a coating on the surface of the film in a thickness of 10  $\mu\text{m}$ . The resulting coated films were combined each other so that the coated surface becomes an inner surface, and then subjected to a high frequency heating adhesion to give a blood bag.

Example 7 (Production of vascular prosthesis)

After the inner/outer surfaces of a vascular prosthesis manufactured by Japan Gore-Tex Co., Ltd. (Gore-Tex EPTFE graft, straight graft, inner diameter: 3 mm, length: 10 cm) were subjected to a glow discharge treatment, the vascular prosthesis was dipped in ethanol to remove air bubble in a cavity under reduced pressure. Thereafter, the vascular prosthesis was coated with a solution of an ethylene-vinyl alcohol copolymer (manufactured by Nippon Synthetic Chemical Industry Co., Ltd., ethylene content: 32 molar %) and cilostazol (contained in an amount of 10 % by weight to a total solid content) in 1,1,1,3,3-hexafluoro-2-propanol (total concentration: 5 % by weight) while circulating the solution by an equipment shown in Fig. 3 to retain the porous structure, thereby to obtain a vascular prosthesis having an anticoagulate coating. The amount of coating to the vascular prosthesis was about 200 mg.

In Fig. 3, a vascular prosthesis 1 is contained in a vacuum chamber 2. To both ends of the vascular prosthesis 1, pipes 5 and 6 for circulation are connected, respectively. The solution 4 of the ethylene-vinyl alcohol copolymer and cilostazol is circulated in the vascular prosthesis 1 using a pump 3 to coat the blood vessel.

Example 8 (Production of blood line for hemodialysis)

The inner surface of a main tube of a blood circuit (CLIRANS Blood Line for hemodialysis) manufactured by Terumo Corporation, was coated

5 with a solution of polyvinyl chloride (comprising 100 parts by weight of polyvinyl chloride having an average degree of polymerization of 1100 and 40 parts by weight of DOP) and cilostazol (contained in an amount of 5 % by weight to a total solid content) in tetrahydrofuran (total concentration: 10 % by weight) by a rotating drum method to produce a blood circuit having an anticoagulant coating of 10  $\mu\text{m}$  in thickness.

Example 9 (Production of blood circuit)

10 Soft polyvinyl chloride [comprising 100 parts by weight of polyvinyl chloride having an average degree of polymerization of 800, 40 parts by weight of DOP, 7 parts by weight of epoxidized soybean oil, 3 parts by weight of a stabilizer (mixture of calcium stearate and zinc stearate) and 0.2 parts by weight of a lubricant] was mixed with cilostazol in the melting condition at a proportion of 5 % by weight of cilostazol to the total amount. By using the above soft polyvinyl chloride containing cilostazol and soft polyvinyl chloride [comprising 100 parts by weight of polyvinyl chloride having an average degree of polymerization of 1700, 70 parts by weight of DOP, 6 parts by weight of epoxidized soybean oil, 2.2 parts by weight of a stabilizer (mixture of calcium stearate and zinc stearate) and 0.1 parts by weight of a lubricant], a two-layer tube having an outer diameter of 7 mm, an inner diameter of 4.5 mm and a thickness of 1.25 mm was produced by a co-extrusion molder equipped with a circular die under a nitrogen atmosphere. The resulting tube was composed of a soft polyvinyl chloride layer (thickness: 1.00 mm) as an outer layer and a cilostazol-containing soft polyvinyl chloride layer (thickness: 0.25 mm) as an inner layer.

Example 10

15 360 Mg of an ethylene-vinyl alcohol copolymer (ethylene content: 32 molar %, manufactured by Nippon Synthetic Chemical Industry Co., Ltd.) and 40 mg of cilostazol were dissolved in 10 ml of 1,1,1,3,3-hexafluoro-2-propanol and the resulting solution was casted on a glass plate, which was dried at room temperature for 8 hour and further dried by a vacuum drier at 40 °C for 24 hours to give a transparent film (thickness: about 50  $\mu\text{m}$ ). The amount of cilostazol of the resulting film was 10 % by weight.

20 100 Mg of the resulting film was collected and then tested according to the same manner as that described in Example 1, 2 and 3. As a result, continuous release of cilostazol in the concentration exceeding the effective concentration was observed, similar to those obtained in Examples 4 and 5.

In this production process, a cloudy film was obtained when the amount of cilostazol exceeds 20 % by weight.

Example 11

360 Mg of poly(methyl methacrylate) (manufactured by Sumitomo Chemical Company, Ltd.) and 40 mg of cilostazol were dissolved in 10 ml of chloroform and the resulting solution was casted on a glass plate, which was dried at room temperature for 8 hours and further dried by a vacuum drier at 40 °C for 24 hours to give a transparent film (thickness: about 50  $\mu$ ).

100 Mg of the resulting film was collected and then tested according to the same manner as that described in Example 1, 2 and 3. As a result, continuous release in the concentration exceeding the effective concentration was observed.

Example 12

360 Mg of an ethylene-vinyl alcohol copolymer (manufactured by Nippon Synthetic Chemical Industry Co., Ltd., ethylene content: 32 molar %) and 40 mg of dipyridamole were dissolved in 10 ml of 1,1,1,3,3-hexafluoro-2-propanol and the resulting solution was casted on a glass plate, which was dried at room temperature for 8 hours and further dried by a vacuum drier at 40 °C for 24 hours to give a transparent film (thickness: about 50  $\mu$ ).

In this production process, a cloudy film was obtained when the amount of dipyridamole exceeds 20 % by weight.

Example 13

An ethylene-vinyl alcohol copolymer (manufactured by Nippon Synthetic Chemical Industry Co., Ltd, ethylene content: 44 molar %) was pulverized by a chemical mill(model R-8) to collect particles having a particle size of 50 to 125  $\mu$ m. 900 Mg of the resulting particles were mixed with 100 mg of dipyridamole and the mixture was pressed by a compact type test press (manufactured by Toyo Seiki Co., Ltd.) at 180 °C for 2 minutes to give a transparent film having a thickness of about 100  $\mu$ m.

In this production process, an opaque film was obtained when the amount of dipyridamole exceeds 20 % by weight.

100 Mg of the respective film obtained in Examples 12 and 13 was collected, respectively, and then tested according to the same manner as that described in Example 1, 2 and 3. As a result, continuous release of dipyridamole in the concentration exceeding the effective concentration (1.8  $\mu$ g/ml) was observed until 8 hours after the begin-

ning of dissolution (see Fig. 4).

Example 14

5 173 Mg of polyvinyl chloride (manufactured by Shin-Etsu Chemical Co., Ltd., KP-13E), 17 mg of DOP and 10 mg of dipyridamole were dissolved in 5 ml of tetrahydrofuran and the resulting solution was flowed and applied on a glass plate, which was dried by a vacuum drier at 40 °C for 24 hours to give a transparent film (thickness: about 50  $\mu$ ).

Example 15

15 Poly(methyl methacrylate) (manufactured by Sumitomo Chemical Company Ltd.) was pulverized by a chemical mill(model R-8) to collect particles having a particle size of 50 to 125  $\mu$ m. 950 Mg of the resulting particles were mixed with 50 mg of dipyridamole and the mixture was pressed by a compact type test press (manufactured by Toyo Seiki Co., Ltd.) at 180 °C for 2 minutes to give a transparent film having a thickness of about 100  $\mu$ m.

20 25 Regarding a relation between a kind of the resin and a dispersed state of the drug as well as a relation between the kind of the resin and release properties of the drug, cilostazol and dipyridamole showed same tendency.

Example 16

30 35 40 45 50 55 60 65 70 75 80 85 90 95 100 105 110 115 120 125 130 135 140 145 150 155 160 165 170 175 180 185 190 195 200 205 210 215 220 225 230 235 240 245 250 255 260 265 270 275 280 285 290 295 300 305 310 315 320 325 330 335 340 345 350 355 360 365 370 375 380 385 390 395 400 405 410 415 420 425 430 435 440 445 450 455 460 465 470 475 480 485 490 495 500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 615 620 625 630 635 640 645 650 655 660 665 670 675 680 685 690 695 700 705 710 715 720 725 730 735 740 745 750 755 760 765 770 775 780 785 790 795 800 805 810 815 820 825 830 835 840 845 850 855 860 865 870 875 880 885 890 895 900 905 910 915 920 925 930 935 940 945 950 955 960 965 970 975 980 985 990 995 1000 1005 1010 1015 1020 1025 1030 1035 1040 1045 1050 1055 1060 1065 1070 1075 1080 1085 1090 1095 1100 1105 1110 1115 1120 1125 1130 1135 1140 1145 1150 1155 1160 1165 1170 1175 1180 1185 1190 1195 1200 1205 1210 1215 1220 1225 1230 1235 1240 1245 1250 1255 1260 1265 1270 1275 1280 1285 1290 1295 1300 1305 1310 1315 1320 1325 1330 1335 1340 1345 1350 1355 1360 1365 1370 1375 1380 1385 1390 1395 1400 1405 1410 1415 1420 1425 1430 1435 1440 1445 1450 1455 1460 1465 1470 1475 1480 1485 1490 1495 1500 1505 1510 1515 1520 1525 1530 1535 1540 1545 1550 1555 1560 1565 1570 1575 1580 1585 1590 1595 1600 1605 1610 1615 1620 1625 1630 1635 1640 1645 1650 1655 1660 1665 1670 1675 1680 1685 1690 1695 1700 1705 1710 1715 1720 1725 1730 1735 1740 1745 1750 1755 1760 1765 1770 1775 1780 1785 1790 1795 1800 1805 1810 1815 1820 1825 1830 1835 1840 1845 1850 1855 1860 1865 1870 1875 1880 1885 1890 1895 1900 1905 1910 1915 1920 1925 1930 1935 1940 1945 1950 1955 1960 1965 1970 1975 1980 1985 1990 1995 2000 2005 2010 2015 2020 2025 2030 2035 2040 2045 2050 2055 2060 2065 2070 2075 2080 2085 2090 2095 2100 2105 2110 2115 2120 2125 2130 2135 2140 2145 2150 2155 2160 2165 2170 2175 2180 2185 2190 2195 2200 2205 2210 2215 2220 2225 2230 2235 2240 2245 2250 2255 2260 2265 2270 2275 2280 2285 2290 2295 2300 2305 2310 2315 2320 2325 2330 2335 2340 2345 2350 2355 2360 2365 2370 2375 2380 2385 2390 2395 2400 2405 2410 2415 2420 2425 2430 2435 2440 2445 2450 2455 2460 2465 2470 2475 2480 2485 2490 2495 2500 2505 2510 2515 2520 2525 2530 2535 2540 2545 2550 2555 2560 2565 2570 2575 2580 2585 2590 2595 2600 2605 2610 2615 2620 2625 2630 2635 2640 2645 2650 2655 2660 2665 2670 2675 2680 2685 2690 2695 2700 2705 2710 2715 2720 2725 2730 2735 2740 2745 2750 2755 2760 2765 2770 2775 2780 2785 2790 2795 2800 2805 2810 2815 2820 2825 2830 2835 2840 2845 2850 2855 2860 2865 2870 2875 2880 2885 2890 2895 2900 2905 2910 2915 2920 2925 2930 2935 2940 2945 2950 2955 2960 2965 2970 2975 2980 2985 2990 2995 3000 3005 3010 3015 3020 3025 3030 3035 3040 3045 3050 3055 3060 3065 3070 3075 3080 3085 3090 3095 3100 3105 3110 3115 3120 3125 3130 3135 3140 3145 3150 3155 3160 3165 3170 3175 3180 3185 3190 3195 3200 3205 3210 3215 3220 3225 3230 3235 3240 3245 3250 3255 3260 3265 3270 3275 3280 3285 3290 3295 3300 3305 3310 3315 3320 3325 3330 3335 3340 3345 3350 3355 3360 3365 3370 3375 3380 3385 3390 3395 3400 3405 3410 3415 3420 3425 3430 3435 3440 3445 3450 3455 3460 3465 3470 3475 3480 3485 3490 3495 3500 3505 3510 3515 3520 3525 3530 3535 3540 3545 3550 3555 3560 3565 3570 3575 3580 3585 3590 3595 3600 3605 3610 3615 3620 3625 3630 3635 3640 3645 3650 3655 3660 3665 3670 3675 3680 3685 3690 3695 3700 3705 3710 3715 3720 3725 3730 3735 3740 3745 3750 3755 3760 3765 3770 3775 3780 3785 3790 3795 3800 3805 3810 3815 3820 3825 3830 3835 3840 3845 3850 3855 3860 3865 3870 3875 3880 3885 3890 3895 3900 3905 3910 3915 3920 3925 3930 3935 3940 3945 3950 3955 3960 3965 3970 3975 3980 3985 3990 3995 4000 4005 4010 4015 4020 4025 4030 4035 4040 4045 4050 4055 4060 4065 4070 4075 4080 4085 4090 4095 4100 4105 4110 4115 4120 4125 4130 4135 4140 4145 4150 4155 4160 4165 4170 4175 4180 4185 4190 4195 4200 4205 4210 4215 4220 4225 4230 4235 4240 4245 4250 4255 4260 4265 4270 4275 4280 4285 4290 4295 4300 4305 4310 4315 4320 4325 4330 4335 4340 4345 4350 4355 4360 4365 4370 4375 4380 4385 4390 4395 4400 4405 4410 4415 4420 4425 4430 4435 4440 4445 4450 4455 4460 4465 4470 4475 4480 4485 4490 4495 4500 4505 4510 4515 4520 4525 4530 4535 4540 4545 4550 4555 4560 4565 4570 4575 4580 4585 4590 4595 4600 4605 4610 4615 4620 4625 4630 4635 4640 4645 4650 4655 4660 4665 4670 4675 4680 4685 4690 4695 4700 4705 4710 4715 4720 4725 4730 4735 4740 4745 4750 4755 4760 4765 4770 4775 4780 4785 4790 4795 4800 4805 4810 4815 4820 4825 4830 4835 4840 4845 4850 4855 4860 4865 4870 4875 4880 4885 4890 4895 4900 4905 4910 4915 4920 4925 4930 4935 4940 4945 4950 4955 4960 4965 4970 4975 4980 4985 4990 4995 5000 5005 5010 5015 5020 5025 5030 5035 5040 5045 5050 5055 5060 5065 5070 5075 5080 5085 5090 5095 5100 5105 5110 5115 5120 5125 5130 5135 5140 5145 5150 5155 5160 5165 5170 5175 5180 5185 5190 5195 5200 5205 5210 5215 5220 5225 5230 5235 5240 5245 5250 5255 5260 5265 5270 5275 5280 5285 5290 5295 5300 5305 5310 5315 5320 5325 5330 5335 5340 5345 5350 5355 5360 5365 5370 5375 5380 5385 5390 5395 5400 5405 5410 5415 5420 5425 5430 5435 5440 5445 5450 5455 5460 5465 5470 5475 5480 5485 5490 5495 5500 5505 5510 5515 5520 5525 5530 5535 5540 5545 5550 5555 5560 5565 5570 5575 5580 5585 5590 5595 5600 5605 5610 5615 5620 5625 5630 5635 5640 5645 5650 5655 5660 5665 5670 5675 5680 5685 5690 5695 5700 5705 5710 5715 5720 5725 5730 5735 5740 5745 5750 5755 5760 5765 5770 5775 5780 5785 5790 5795 5800 5805 5810 5815 5820 5825 5830 5835 5840 5845 5850 5855 5860 5865 5870 5875 5880 5885 5890 5895 5900 5905 5910 5915 5920 5925 5930 5935 5940 5945 5950 5955 5960 5965 5970 5975 5980 5985 5990 5995 6000 6005 6010 6015 6020 6025 6030 6035 6040 6045 6050 6055 6060 6065 6070 6075 6080 6085 6090 6095 6100 6105 6110 6115 6120 6125 6130 6135 6140 6145 6150 6155 6160 6165 6170 6175 6180 6185 6190 6195 6200 6205 6210 6215 6220 6225 6230 6235 6240 6245 6250 6255 6260 6265 6270 6275 6280 6285 6290 6295 6300 6305 6310 6315 6320 6325 6330 6335 6340 6345 6350 6355 6360 6365 6370 6375 6380 6385 6390 6395 6400 6405 6410 6415 6420 6425 6430 6435 6440 6445 6450 6455 6460 6465 6470 6475 6480 6485 6490 6495 6500 6505 6510 6515 6520 6525 6530 6535 6540 6545 6550 6555 6560 6565 6570 6575 6580 6585 6590 6595 6600 6605 6610 6615 6620 6625 6630 6635 6640 6645 6650 6655 6660 6665 6670 6675 6680 6685 6690 6695 6700 6705 6710 6715 6720 6725 6730 6735 6740 6745 6750 6755 6760 6765 6770 6775 6780 6785 6790 6795 6800 6805 6810 6815 6820 6825 6830 6835 6840 6845 6850 6855 6860 6865 6870 6875 6880 6885 6890 6895 6900 6905 6910 6915 6920 6925 6930 6935 6940 6945 6950 6955 6960 6965 6970 6975 6980 6985 6990 6995 7000 7005 7010 7015 7020 7025 7030 7035 7040 7045 7050 7055 7060 7065 7070 7075 7080 7085 7090 7095 7100 7105 7110 7115 7120 7125 7130 7135 7140 7145 7150 7155 7160 7165 7170 7175 7180 7185 7190 7195 7200 7205 7210 7215 7220 7225 7230 7235 7240 7245 7250 7255 7260 7265 7270 7275 7280 7285 7290 7295 7300 7305 7310 7315 7320 7325 7330 7335 7340 7345 7350 7355 7360 7365 7370 7375 7380 7385 7390 7395 7400 7405 7410 7415 7420 7425 7430 7435 7440 7445 7450 7455 7460 7465 7470 7475 7480 7485 7490 7495 7500 7505 7510 7515 7520 7525 7530 7535 7540 7545 7550 7555 7560 7565 7570 7575 7580 7585 7590 7595 7600 7605 7610 7615 7620 7625 7630 7635 7640 7645 7650 7655 7660 7665 7670 7675 7680 7685 7690 7695 7700 7705 7710 7715 7720 7725 7730 7735 7740 7745 7750 7755 7760 7765 7770 7775 7780 7785 7790 7795 7800 7805 7810 7815 7820 7825 7830 7835 7840 7845 7850 7855 7860 7865 7870 7875 7880 7885 7890 7895 7900 7905 7910 7915 7920 7925 7930 7935 7940 7945 7950 7955 7960 7965 7970 7975 7980 7985 7990 7995 8000 8005 8010 8015 8020 8025 8030 8035 8040 8045 8050 8055 8060 8065 8070 8075 8080 8085 8090 8095 8100 8105 8110 8115 8120 8125 8130 8135 8140 8145 8150 8155 8160 8165 8170 8175 8180 8185 8190 8195 8200 8205 8210 8215 8220 8225 8230 8235 8240 8245 8250 8255 8260 8265 8270 8275 8280 8285 8290 8295 8300 8305 8310 8315 8320 8325 8330 8335 8340 8345 8350 8355 8360 8365 8370 8375 8380 8385 8390 8395 8400 8405 8410 8415 8420 8425 8430 8435 8440 8445 8450 8455 8460 8465 8470 8475 8480 8485 8490 8495 8500 8505 8510 8515 8520 8525 8530 8535 8540 8545 8550 8555 8560 8565 8570 8575 8580 8585 8590 8595 8600 8605 8610 8615 8620 8625 8630 8635 8640 8645 8650 8655 8660 8665 8670 8675 8680 8685 8690 8695 8700 8705 8710 8715 8720 8725 8730 8735 8740 8745 8750 8755 8760 8765 8770 8775 8780 8785 8790 8795 8800 8805 8810 8815 8820 8825 8830 8835 8840 8845 8850 8855 8860 8865 8870 8875 8880 8885 8890 8895 8900 8905 8910 8915 8920 8925 8930 8935 8940 8945 8950 8955 8960 8965 8970 8975 8980 8985 8990 8995 9000 9005 9010 9015 9020 9025 9030 9035 9040 9045 9050 9055 9060 9065 9070 9075 9080 9085 9090 9095 9100 9105 9110 9115 9120 9125 9130 9135 9140 9145 9150 9155 9160 9165 9170 9175 9180 9185 9190 9195 9200 9205 9210 9215 9220 9225 9230 9235 9240 9245 9250 9255 9260 9265 9270 9275 9280 9285 9290 9295 9300 9305 9310 9315 9320 9325 9330 9335 9340 9345 9350 9355 9360 9365 9370 9375 9380 9385 9390 9395 9400 9405 9410 9415 9420 9425 9430 9435 9440 9445 9450 9455 9460 9465 9470 9475 9480 9485 9490 9495 9500 9505 9510 9515 9520 9525 9530 9535 9540 9545 9550 9555 9560 9565 9570 9575 9580 9585 9590 9595 9600 9605 9610 9615 9620 9625 9630 9635 9640 9645 9650 9655 9660 9665 9670 9675 9680 9685 9690 9695 9700 9705 9710 9715 9720 9725 9730 9735 9740 9745 9750 9755 9760 9765 9770 9775 9780 9785 9790 9795 9800 9805 9810 9815 9820 9825 9830 9835 9840 9845 9850 9855 9860 9865 9870 9875 9880 9885 9890 9895 9900 9905 9910 9915 9920 9925 9930 99

## Example 18

360 Mg of poly(methyl methacrylate) (manufactured by Sumitomo Chemical Company Ltd.) and 40 mg of aspirin were dissolved in 10 ml of chloroform and the resulting solution was casted on a glass plate, which was dried at room temperature for 8 hours and further dried by a vacuum drier at 40 °C for 24 hours to give a transparent film having a thickness of about 50 µm.

Regarding a relation between a kind of the resin and a dispersed state of the drug as well as a relation between the kind of the resin and release properties of the drug, aspirin and cilostazol showed same tendency.

100 Mg of the film obtained in Example 18 was collected and then tested according to the same manner as that described in Example 1, 2 and 3. As a result, continuous release of aspirin in the concentration exceeding the effective concentration (1 µg/ml) was observed until 8 hours after the beginning of dissolution (see Fig. 5)

## Example 19 (Production of vascular stent)

500 Mg of a Palmaz-Shatz stent (manufactured by Johnson & Johnson Co., U.S.A.) was dipped in an ethylene-vinyl alcohol copolymer-cilostazol solution [prepared by dissolving 500 mg of an ethylene-vinyl alcohol copolymer (manufactured by Nippon Synthetic Chemical Industry Co., Ltd., Soarnol K3825N) and 500 mg of cilostazol in 100 ml of hexafluoro-2-propanol, amount of cilostazol: 50 % by weight] and, after air-drying, the stent was dipped and air-dried again. This operation was repeated to produce a coating layer (amount of cilostazol: 50 % by weight) having a thickness of about 50 µm. The resulting coated stent was dried at 40 °C for 72 hours under vacuum to remove the solvent completely. Thereafter, it was dipped in an ethylene-vinyl alcohol copolymer-cilostazol solution [newly prepared by dissolving 950 mg of an ethylene-vinyl alcohol copolymer (manufactured by Nippon Synthetic Chemical Industry Co., Ltd., Soarnol K3825N) and 50 mg of cilostazol in 100 ml of 1,1,1,3,3,3-hexafluoro-2-propanol] and then air-dried. This operation was repeated to produce a second coating layer (amount of cilostazol: 5 % by weight) on the above coating layer.

## Example 20 (Production of stent)

An ethylene-vinyl alcohol copolymer (manufactured by Kuraray Co., Ltd., ethylene content: 44 molar %) was pulverized by a pulverizer (manufactured by Fritsch Co., rotor speed mill) to collect particles having a particle size of 50 to 125 µm. Then, 45g of the particles were dryblended with 5

g of cilostazol (manufactured by Otsuka Pharmaceutical Co., Ltd.) and the mixture was extruded with kneading at 180 °C under a nitrogen atmosphere by an extruder (manufactured by CSI Co., CS-194A MAX MIXING EXTRUDER). Thereafter, the extrudate was stretched to produce an ethylene-vinyl alcohol copolymer filament having a size of 0.25 µm in diameter, wherein cilostazol is uniformly dispersed. The amount of cilostazol in the resulting copolymer filament was 10 % by weight.

16 Filaments were interwound to produce a self-expanding type stent (wall type stent) having a length of 2 cm, an outer diameter on expansion of 2.5 mm and an outer diameter on shrinkage of 1.4 mm.

## Example 21 (Production of catheter)

1.8 G of poly(methyl methacrylate) (manufactured by Sumitomo Chemical Company Ltd.) and 0.2 g of cilostazol (manufactured by Otsuka Pharmaceutical Co., Ltd.) were dissolved in 100 ml of chloroform. The resulting solution was coated on the inner and outer surfaces of a single lumen catheter having an inner diameter of 1.2 mm, an outer diameter of 2.0 mm and a length of 70 cm, which was prepared in advance by molding soft polyvinyl chloride, in the coating thickness of about 100 µm.

## Example 22 (Production of blood circuit connector)

Poly(methyl methacrylate) (manufactured by Sumitomo Chemical Company Ltd.) was pulverized by a pulverizer (manufactured by Fritsch Co., rotor speed mill) and screened to collect particles having a particle size of 50 to 125 µm. Then, 95g of the particles were dryblended with 5 g of cilostazol and the blend was extruded with kneading at 180 °C under a nitrogen atmosphere by an extruder (manufactured by CSI Co., CS-194A MAX MIXING EXTRUDER) using a strand die. After the extrudate was pelletized, a blood circuit connector 10 for pump-oxygenator having the shape shown in Fig. 6 was produced by an injection molding using a midget molder.

## Claims

1. A medical material comprising a polymer or copolymer of a vinyl derivative having a polar group, said polymer or copolymer containing an antiplatelet agent.
2. The medical material according to claim 1, wherein the polar group is a hydroxyl group, a chlorine atom, a cyano group or an alkoxy-

bonyl group.

3. The medical material according to claim 1, wherein the polar group is a hydroxyl group, a chlorine atom or an alkoxy carbonyl group.

4. The medical material according to claim 1, wherein the polar group is a hydroxyl group, a lower alkoxy carbonyl group or a chlorine atom.

5. The medical material according to claim 1, wherein the polymer or copolymer is polyvinyl chloride, ethylene-vinyl alcohol copolymer, polyacrylonitrile, polymethacrylate or polyacrylate.

6. The medical material according to claim 1, wherein the polymer or copolymer is polyvinyl chloride, polymethacrylate or ethylene-vinyl alcohol copolymer.

7. The medical material according to claim 1, wherein the polymer or copolymer is an ethylene-vinyl alcohol copolymer.

8. The medical material according to claim 1, wherein the amount of the antiplatelet agent is 0.01 to 60 parts by weight based on 100 parts by weight of the medical material.

9. The medical material according to claim 8, wherein the amount of the antiplatelet agent is 1 to 44.4 parts by weight based on 100 parts by weight of the medical material.

10. The medical material according to claim 9, wherein the amount of the antiplatelet agent is 4.8 to 33.3 parts by weight based on 100 parts by weight of medical material.

11. The medical material according to claim 1, wherein the amount of the antiplatelet agent is not more than 20 % by weight based on the total weight.

12. The medical material according to claim 1, wherein the antiplatelet agent is at least one selected from the group consisting of cilostazol, dipyridamole, beraprost, satigrel and aspirin.

13. A medical material comprising a polymer or copolymer of a vinyl derivative having a polar group, said polymer or copolymer containing cilostazol.

14. The medical material according to claim 13, wherein the amount of cilostazol is 0.01 to 60 parts by weight based on 100 parts by weight of the medical material.

15. The medical material according to claim 14, wherein the amount of cilostazol is 1 to 44.4 parts by weight based on 100 parts by weight of the medical material.

16. The medical material according to claim 15, wherein the amount of cilostazol is 4.8 to 33.3 parts by weight based on 100 parts by weight of the medical material.

17. The medical material according to claim 13, wherein the amount of cilostazol is not more than 20 % by weight based on the total weight.

18. The medical material according to claim 13, 14, 15, 16 or 17, wherein the polymer or copolymer is polyvinyl chloride, ethylene-vinyl alcohol copolymer, polyacrylonitrile, polymethacrylate or polyacrylate.

19. The medical material according to claim 18, wherein the polymer or copolymer is an ethylene-vinyl alcohol copolymer.

20. The medical material according to claim 21, wherein the ethylene-vinyl alcohol copolymer contains cilostazol.

21. The medical material according to claim 20, wherein the amount of cilostazol is not more than 20 % by weight based on the total weight.

22. A medical material wherein a polymer or copolymer of a vinyl derivative having a polar group and cilostazol are mixed in a molten state.

23. The medical material according to claim 22, wherein the polymer or copolymer is an ethylene-vinyl alcohol copolymer.

24. A process for producing a medical material which comprises mixing a polymer or copolymer of a vinyl derivative having a polar group with an antiplatelet agent in a molten state.

25. A process for producing a medical material which comprises dissolving a polymer or copolymer of a vinyl derivative having a polar group and an antiplatelet agent in a solvent and then removing the solvent.

26. The medical material according to claim 1 to 13, 20 or 21, wherein the medical material is a

material for medical device.

27. A process for producing the medical material of claim 24 or 25, wherein the medical material is a material for medical device. 5

28. A process for producing the medical material of claim 24 or 25, wherein an antiplatelet agent is cilostazol. 10

29. The process for producing a medical material according to claim 27, wherein the antiplatelet agent is cilostazol.

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FIG. 1

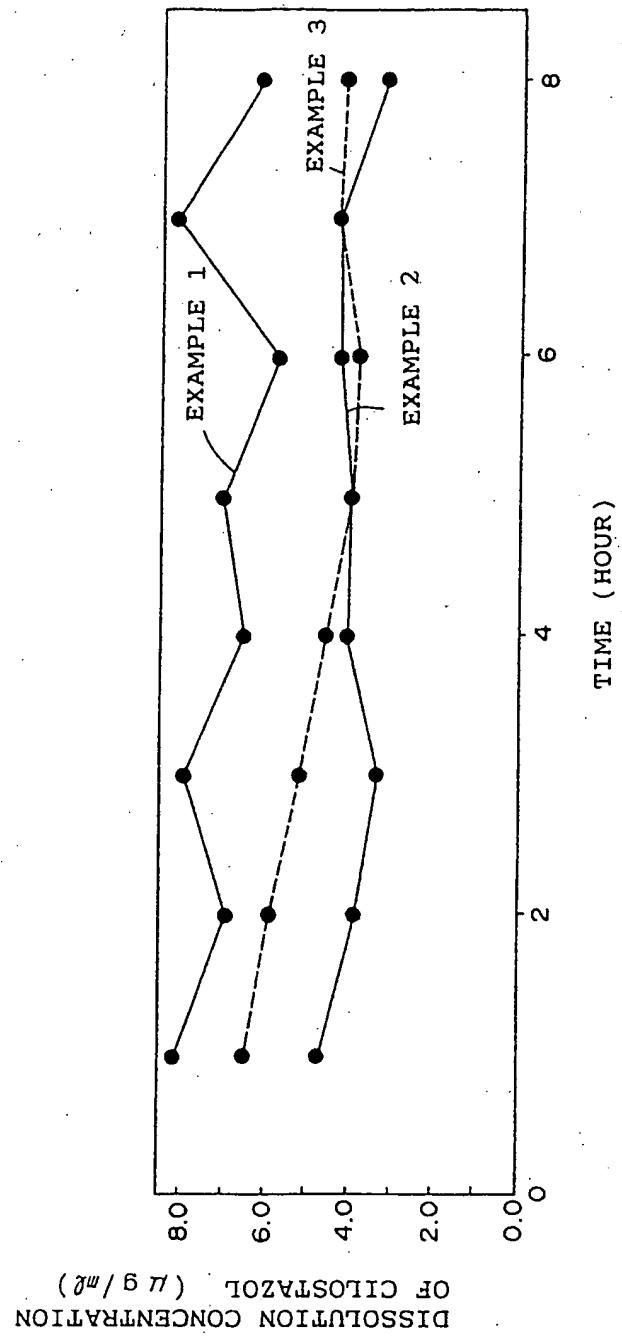


FIG. 2

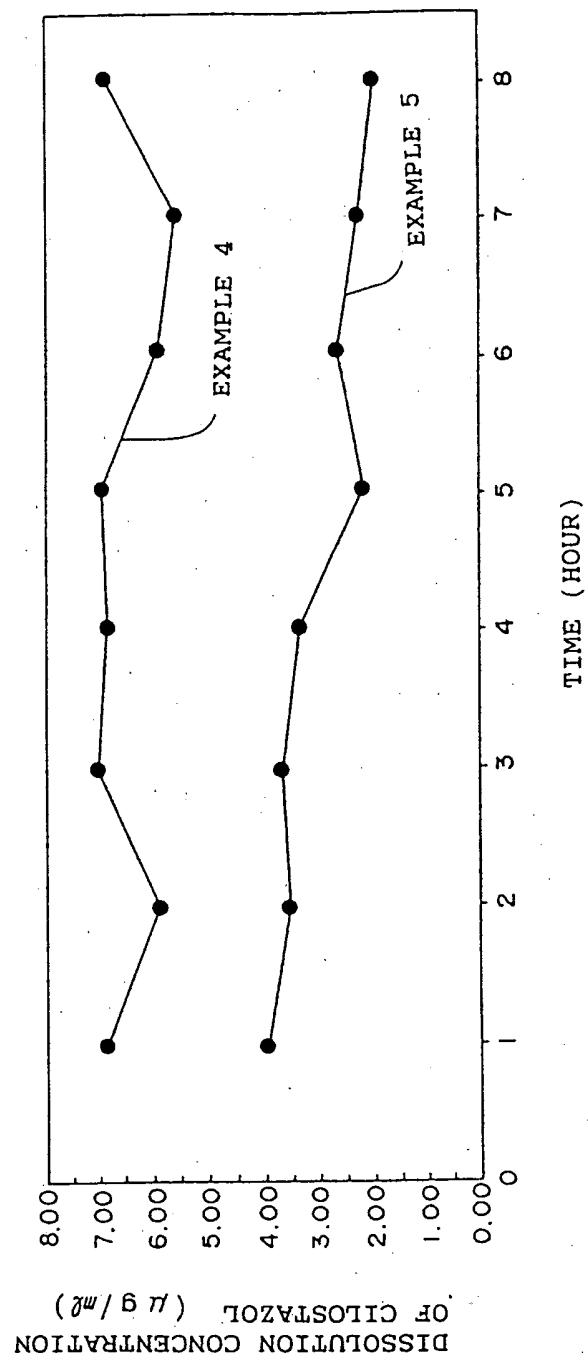


FIG. 3

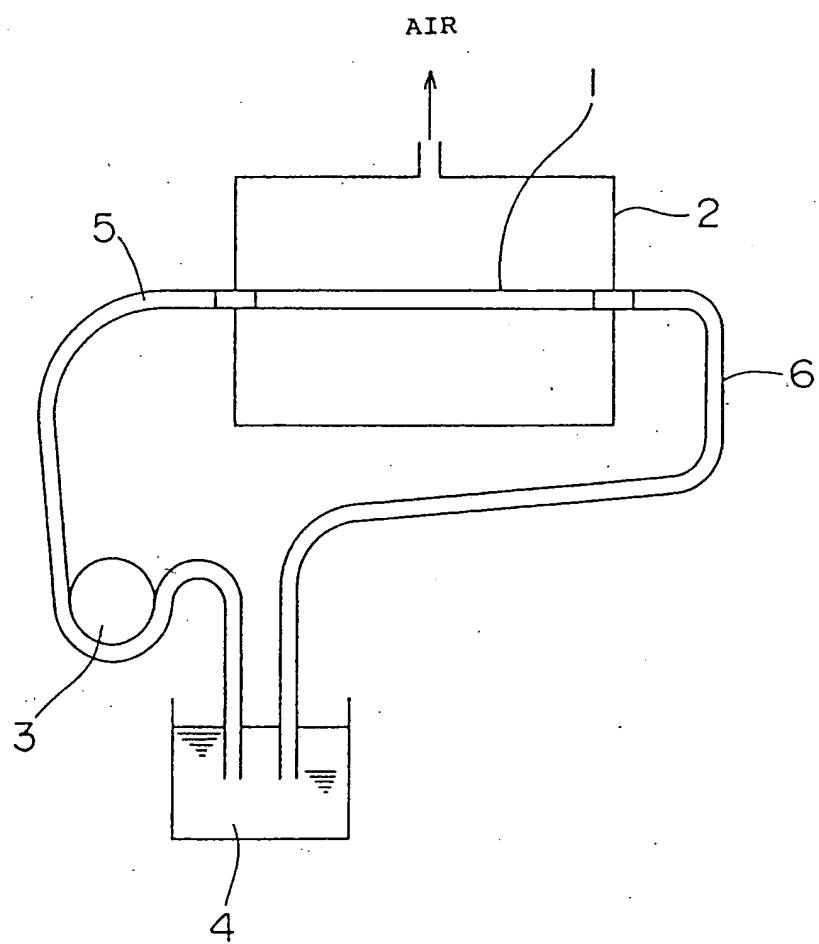


FIG. 4

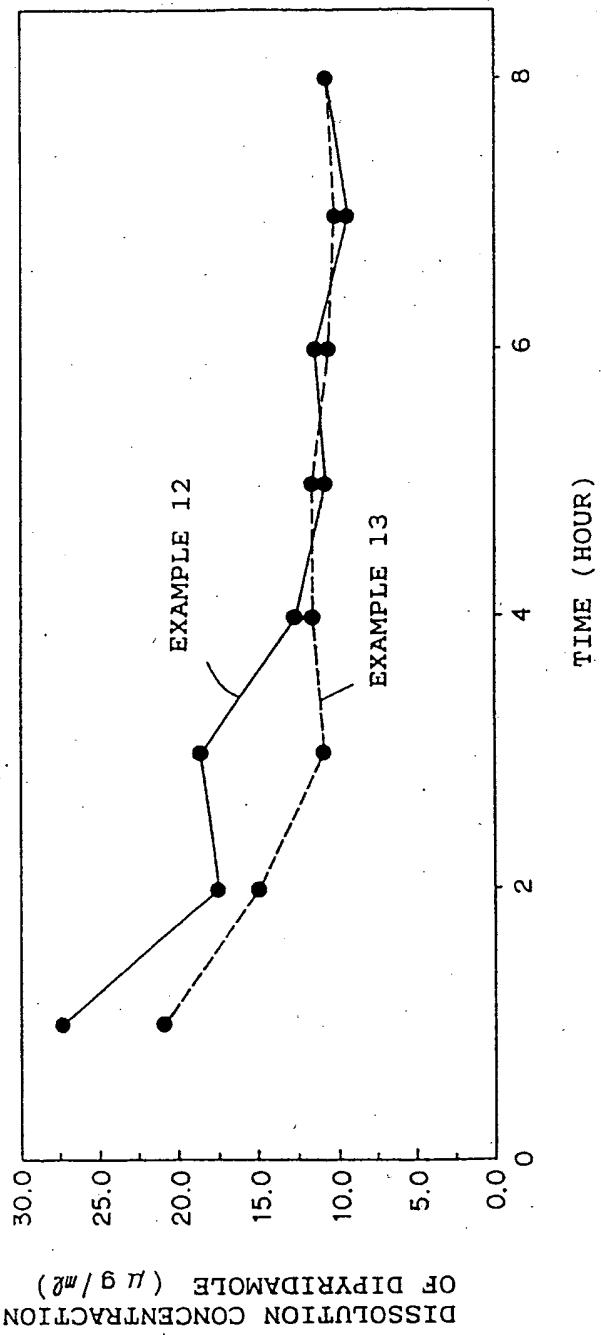


FIG. 5

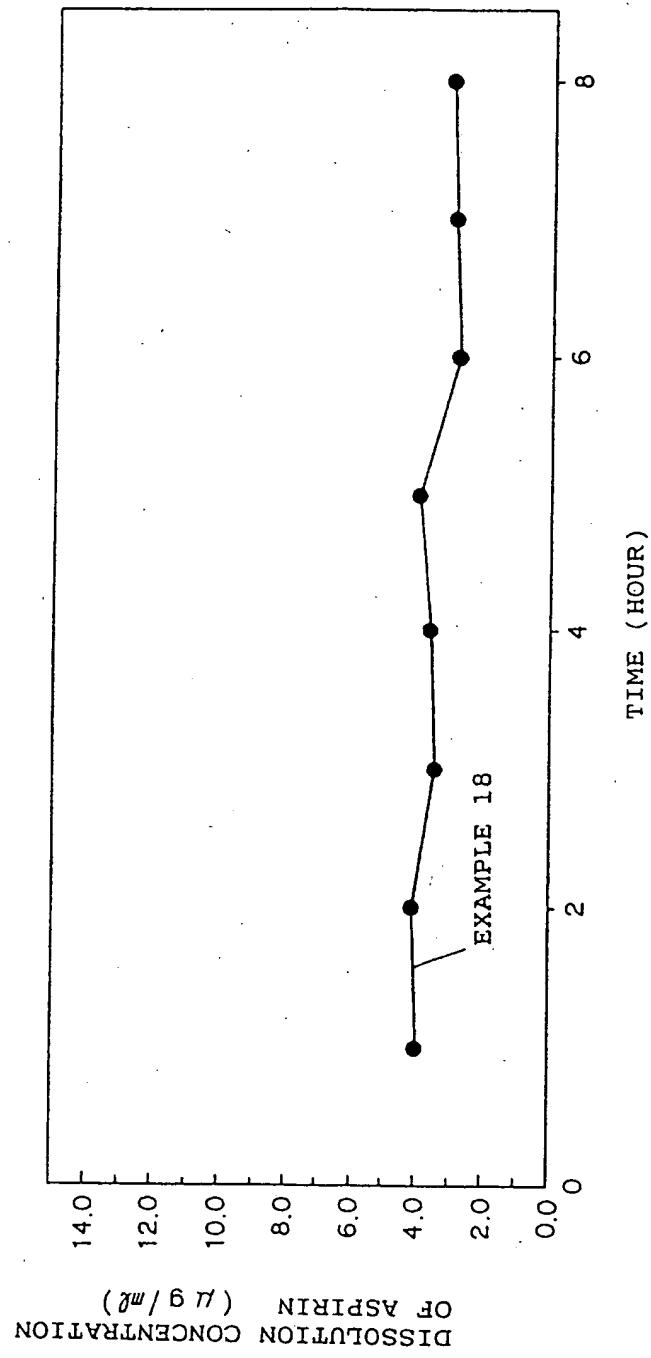


FIG. 6(a)

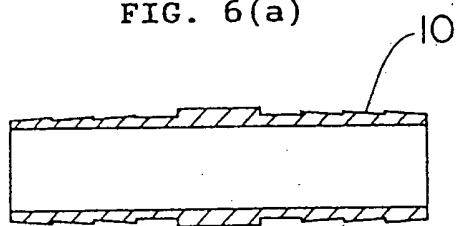


FIG. 6(b)

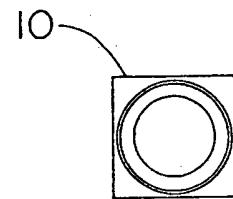
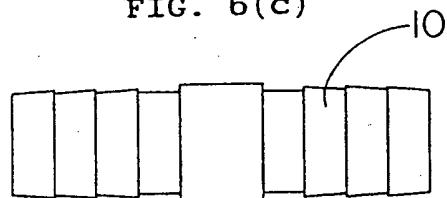


FIG. 6(c)



## INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP94/01162

<b>A. CLASSIFICATION OF SUBJECT MATTER</b>		
Int. Cl <sup>6</sup> A61L33/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
<b>B. FIELDS SEARCHED</b>		
Minimum documentation searched (classification system followed by classification symbols)		
Int. Cl <sup>5</sup> A61L27/00-33/00		
Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Jitsuyo Shinan Koho 1925 - 1994 Kokai Jitsuyo Shinan Koho 1971 - 1994		
Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)		
<b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b>		
Category <sup>a</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X Y	JP, A, 54-135494 (Asahi Chemical Industry Co., Ltd.), October 20, 1979 (20. 10. 79), (Family: none)	1-11, 25-27 12-24, 28, 29
X Y	JP, A, 62-217970 (Sumitomo Bakelite Co., Ltd.), September 25, 1987 (25. 09. 87), (Family: none)	1-11, 25-27 12-24, 28, 29
Y	JP, A, 2-234767 (Bector Dickinson and Co.), September 17, 1990 (17. 09. 90), (Family: none)	22-24, 27-29
<input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed		
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search	Date of mailing of the international search report	
October 11, 1994 (11. 10. 94)	November 1, 1994 (01. 11. 94)	
Name and mailing address of the ISA/ Japanese Patent Office	Authorized officer	
Facsimile No.	Telephone No.	

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